REMARKS

Support for the amendments to claims 1 and 24 can be found throughout the instant application including the Drawings and claims as originally filed. No new matter has been added.

Specific support for adding EPCR and thrombomodulin language can be found at pg. 7, last paragraph as well as elsewhere under the Summary of the Invention. See also pg. 22, lines 5-24 (disclosing particular NF κB inhibitors such as IκB and other inhibitors). Administration of agent combinations is provided on pg. 6, lines 1-8 and pg. 14, lines 12-17, for example.

Particular support for language relating to *ex vivo* and direct injection administration can be found at pg. 10, first paragraph. See also pg. 23, first full paragraph (disclosing a variety of administration methods including direct cell microinjection).

Support for specified fragments of EPCR, thrombomodulin and NF- κB inhibitor can be found throughout the current application. See pg. 17, line 13 to pg. 18, line 28; pg. 20, line 4 to pg. 21, line 11; and pg. 22, lines 21-24.

Claim 7 was objected to because the word "claim" was missing. The objection has been addressed by this submission.

Claims 1-28 stand rejected under 35 USC §112, first paragraph, on grounds that the specification does not provide an adequate description of agents capable of enhancing APC. The USPTO acknowledged that recitation of thrombomodulin and EPCR in the claims would satisfy basis for the rejection. Action at pg. 5, first full paragraph.

Although Applicants must respectfully disagree with the rejection, grounds for it have been addressed by this submission.

The present application discloses a variety of APC enhancing agents in addition to the thrombomodulin and EPCR cited by the USPTO. See eg., pg. 22, lines 5-25. These additional agents could be used by a worker in the field to practice the claimed invention. Thus there is no basis for the present rejection. However in the interest of furthering prosecution, claims 1 and 24 have been amended to point out use of thrombomodulin, EPCR and functional fragments thereof. See pg. 17, line 1 to pg. 21, last line (disclosing a wide range of suitable thrombomodulin and EPCR sequences as well as functional fragments thereof).

Accordingly, reconsideration and withdrawal of the rejection are requested.

Claims 1-28 stand rejected under 35 USC §112, first paragraph, on grounds set forth on pgs. 5-6, bridging paragraph. Applicants disagree with the rejection as formulated. However, basis for it has been addressed by this submission. Specifically, claims 1 and 24 have been amended to point out more particular administration routes ie., *ex vivo* and direct injection.

On pgs. 6-7 of the Action (bridging paragraph), the USPTO set forth a basis for evaluating claim 24. Respectfully, that basis is flawed. MPEP 2164.01c, as cited in the Action, relates to a product claim limited by a particular use. However, claim 24 is a method. It is not a product claim limited by a use. Reconsideration of this basis for evaluating the patentability of claim 24 is requested.

Claims 1-28 also stand rejected on grounds that "the specification is silent regarding whether the increased graft APC has translated to **clinical benefit**, eg., an

increased graft survival or resistant to graft closure". Action at pg. 7, first full paragraph (emphasis added).

As an initial matter, it is noted that Applicants are under no obligation to submit clinical information to obtain a U.S patent. Nevertheless, the present application fully satisfies the "how to make" and "how to use" requirements of USC §112, first paragraph.

For instance, Applicant's disclosure provides that enhancing activated protein C (APC) levels in vessel grafts helps patency and reduces graft failure. See pgs. 5-6, bridging paragraph. Particular agents for increasing APC include TM and EPCR. See pgs. 6-7. The Summary of the Invention and Detailed Description section provide numerous methods for achieving such enhanced APC levels.

Specific relationship between increasing APC and obtaining better graft patency and reduced failure is exemplified by the Example section.

For instance, Example 3 and Figure 5 show an important inverse relationship between loss of capacity to activate APC and increased amount of thrombin activity. That is, more APC is associated with less thrombin activity and graft damage. Examples 1 and 2 show that diminished thromboresistance (facilitated by reduced TM expression) increases thrombin production and graft failure. See also Figure 3. The claimed invention addresses this problem by preventing or treating graft failure by restoring or enhancing APC (and reducing thrombin production) by administering particular agents to the graft. See claims 1 and 24 (as amended).

Claims 1-28 were also rejected on grounds that the cited Quyang et al., ("Ouyang") and Kim et al. references (see pg. 8 of the Action) allegedly show that "graft survival does not correlate well with levels of TM". As cited, the references were

published well after the priority date of the instant case. This ground of rejection is improper and should be withdrawn. The issue of whether an applicant's specification is enabling is decided by reference to the application filing date. Information that is available to the public after that date cannot be considered in determining disclosure sufficiency under 35 USC §112. See *Ajinomoto Co., Inc. v. Archer Daniels-Midland Co.*, 228 F.3d 1338, 1345, 56 USPQ2d 1332 (Fed. Cir. 2000), cert denied, 121 S. Ct. 1957 (2001).

Applicants respectfully disagree with the PTO's citation of the Ouyang et al. and Kim et al references on other grounds.

Ouyang et al is an abstract that reports no statistically significant difference between plasma levels of **soluble thrombomodulin (sTM)** in the presence or absence of SVG disease. See the Table. However, Applicants method for treating a vascular graft does not feature sTM. Rather, it involves introducing into cells of the graft nucleic acid that encodes thrombomodulin: a **membrane-associated protein.** See pg. 2, lines –11, of the specification for instance, and references cited therein. Ouyang et al's sTM is not indicative of the amount of thrombomodulin expressed in Applicant's method. Accordingly, the reference, as relied on in the rejection, is not germane to the claimed invention.

There is general recognition that vascular graft failure is divided into early and late stages. Usually, early graft failure is due to occlusive thrombosis while late stage failure is due to neointimal hyperplasia (see Applicant's specification at pg. 1, lines 29-33, for instance). As cited, Kim et al. merely points out that increased levels of TM and APC did not seem to result in a reduction in late stage neointimal formation. However, that report does not preclude a beneficial effect on early stage vein graft failure. As provided by the instant specification at pg. 4, line 28 to pg. 5, line 15, for instance,

Applicants found that by restoring capacity to generate APC by supplying TM, it is possible to prevent local thrombin generation (prerequisite for occlusive thrombosis). Kim et al, as cited, supports this concept. See eg., the Abstract and Introduction of that reference (reporting that TM is a major contributor to early vein graft thromboresistance and that reduced expression thereof facilitates unwanted thrombin production and occlusion). Accordingly, the Kim et al reference, as relied on, does nothing to support the instant rejection under 35 USC §112.

Claims 6-12 stand rejected on grounds that the disclosure "fails to disclose that the method could achieve such outcome". Action at pg. 8. Respectfully, the rejection is improper. The USPTO is challenging the utility of the claimed invention under the guise of §112, first paragraph, without offering any evidence that the claimed invention is inoperable. On this basis alone, this ground of rejection should be withdrawn.

Moreover, even if the Office takes the position that the utility of claims 6-12 is not being challenged, the rejection still fails to withstand scrutiny. Applicants' specification fully satisfies the "how to make" and "how to use" requirement with respect to claims 6-12. For instance, see Applicants' specification at pg. 7, lines 12-14; pg. 8, lines 1-7; pg. 16, lines 7-12; pg. 26, lines 7-24 (disclosing use of the invention to treat atherosclerosis). See also Example 5 showing successful enhancement of APC expression and better graft patency in a rabbit vein graft model of atherosclerosis (as provided in Example 1).

On pgs. 8-10 of the Office Action, the USPTO took the position that "gene transfer in vivo, vector targeting to desired tissues in vivo continues to be unpredictable". Action at pg. 8.

As an initial matter, the references cited on pg. 9 of the Action are not relevant to Applicants' invention. Numerous successful gene transfer experiments have been

published in field of vascular therapy. See Applicants' specification from pg. 3, line 29 to pg. 4, line 25, for instance (providing reference to 14 research articles and 1 US patent relating to success in the field of vascular gene therapy).

Further, claims 1 and 24 have been amended to point out administration routes that are not germane to the references relied on at pgs. 9-10 of the Action.

In view thereof, reconsideration and withdrawal of the outstanding §112, first paragraph, rejections are requested.

Claims 1-28 stand rejected under 35 USC §112, second paragraph, for reciting "susceptible cells". Basis for the rejection has been addressed by this submission.

Claims 1-6, 8-22, and 24-27 stand rejected as being anticipated by French et al. (US Pat. No. 6,290,949). Claims 1-6 and 8-28 were also rejected as being obvious in view of the French patent taken with Larson et al. (U.S Pat. No. 6,309,380). Applicants disagree with the rejection. However, grounds for it have been addressed by this submission.

Basis for the rejections are considered together in the interest of brevity.

As amended, claims 1 and 24 feature methods in which at least one of the administered agents is endothelial cell protein C receptor (EPCR), human IκB factor; or a functional fragment thereof. In contrast, the French patent as relied on does not teach such an agent. Accordingly, there is no basis for an anticipation rejection.

The Larson patent, as cited, fails to remedy this defect. There is no teaching or suggestion in Larson either taken alone or together with French that lead one to practice a

vascular graft treatment method in which at least one of the administered agents is endothelial cell protein C receptor (EPCR), human IκB factor; or a functional fragment thereof. Thus, there is no grounds for an obviousness rejection.

In view thereof, reconsideration and withdrawal of the rejections under §102 and §103 are requested.

It is believed that the application is in condition for allowance, which action is earnestly solicited. Although it is not believed that any fee is needed to consider this submission, the USPTO is authorized to charge our deposit account no. **04-1105** should such fee be deemed necessary.

Attached to this submission is a marked-up version of the changes made to the specification and claims. The attached page is captioned "version with markings to show changes made".

Respectfully submitted,

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By: _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 2 and 13 have been canceled.

Claims 1, 7 and 24 have been amended as follows:

1. (Amended) A method for treating a vascular graft comprising,

a) introducing into [susceptible] cells of the graft an effective amount of at least one nucleic acid encoding at least one of the following agents: endothelial cell protein C receptor (EPCR), thrombomodulin, NF-κB inhibitor ; or a functional fragment thereof [agent that increases activated protein C (APC) activation in the graft],

b) expressing the agent in the cells; and

c) increasing the APC sufficient to treat the graft, wherein at least one of the administered agents is endothelial cell protein C receptor (EPCR), the NF-κB inhibitor; or a functional fragment thereof, and step a) of the method is performed *ex vivo* or by direct injection into the graft.

7. (Amended) The method of claim 6, wherein the transplanted blood vessel (graft) exhibits at least about a 10% decrease in neointima formation in the assay compared to a control vessel.

24. (Amended) A method for engineering a vascular graft that resists failure, the method comprising:

a) introducing into [susceptible] cells of the graft an effective amount of at least one nucleic acid encoding at least one of the following agents: endothelial

cell protein C receptor (EPCR), thrombomodulin, NF-κB inhibitor; or a functional fragment thereof [agent that increases protein C activation in cells of a blood vessel],

b) expressing the agent in the cells; and

c) increasing the APC in the graft sufficient to resist graft failure,

wherein at least one of the administered agents is endothelial cell protein C receptor (EPCR), NF-κB inhibitor; or a functional fragment thereof, and step a) of the method is performed *ex vivo* or by direct injection into the blood vessel.